CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021883Orig1s000

SUMMARY REVIEW

Division Director Memo

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Patient	Division Director Memo
NDA #	21883
Applicant Name	Durata Therapeutics
Date of Submission	September 26, 2013
PDUFA Goal Date	May 26, 2014
Established (USAN) Name	Dalbavancin Injection
Dosage Forms / Strength	Sterile lyophilized powder, 500 mg dalbavancin/vial
Proposed Indications	Acute Bacterial Skin and Skin Structure Infections
Recommended Action:	Approval

Material Reviewed/Consulted Action Package including:	**Names of Discipline Reviewers**
Cross-Discipline Team Leader Review	John Alexander MD MPH
Pharmacology Toxicology Review	Terry Miller PhD
Chemistry Manufacturing and Controls Review	Mark Seggel PhD, Balajee Shanmugam PhD
Medical Officer Review	Dmitri Iarikov MD PhD
Statistical Review	Christopher Kadoorie PhD
Risk Management	Robert Pratt Pharm D
Product Quality Review	Steven Donald MS
Microbiology Review	Peter Coderre PhD, MBA
Clinical Pharmacology Review	Yang He PhD
Office of Scientific Investigations	Lauren Iacono-Connors PhD
Division of Medication Error Prevention and Analysis	Aleksander Winiarski Pharm D
Thorough QT Study Review	Interdisciplinary Review Team
Labeling Reviews	Christine Corser Pharm D, Aleksander Winiarski Pharm D
Division of Good Manufacturing Practice Assessment	Steven Hertz

1.0 Introduction

NDA 21883, Dalbavancin for Injection was submitted by Durata Therapeutics, Inc. on September 26, 2013 for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus, Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus anginosus* group (including *S. anginosus, S. intermedius, S. constellatus*). Dalbavancin is a lipoglycopeptide antibacterial drug that interrupts bacterial cell wall synthesis by binding to D-alanyl-D-alanine terminus in cell wall peptidoglycan.

2.0 Background

NDA 21883 was originally submitted by Vicuron Pharmaceuticals on December 21, 2004 for the treatment of complicated skin and skin structure infections (cSSSI). An approvable letter was issued on September 21, 2005 pending resolution of a chemistry and manufacturing issue and agreement on final labeling. A second approvable letter was issued on June 21, 2006 due to outstanding Chemistry Manufacturing and Controls (CMC) issues. On December 20, 2007, a third approvable letter was issued. One of the deficiencies listed in the letter was that an adequate justification for a noninferiority margin had not been provided for Study VER001-8 and hence the application lacked evidence from a second adequate well-controlled study to support the proposed indication of cSSSI. On September 15, 2008, Pfizer informed the FDA of its intent to withdraw NDA 21883 and of their plans to conduct a second Phase 3 clinical trial of dalbavancin in the treatment of cSSSI.

On December 11, 2009, Durata assumed ownership of NDA 21883 and subsequently initiated a clinical development program that included two new Phase 3 trials in ABSSSI.

Dalbavancin was granted qualified infectious disease product (QIDP) designation for treatment of ABSSSI on October 25, 2012. Dalbavancin was granted fast track designation in 2003. Under the provisions of Generating Antibiotic Incentives Now (GAIN), new drug applications for products with a QIDP designation receive a priority review. As dalbavancin has QIDP designation, it received a priority review. The NDA is also eligible for 5 additional years of marketing exclusivity under GAIN.

The review team has completed their reviews of this application. For a detailed discussion of NDA 21883, please refer to the discipline specific reviews and the Cross-Discipline Team Leader review.

3.0 Product Quality

The Chemistry, Manufacturing and Controls (CMC) reviewers for this application are Balajee Shanmugam, Ph.D., and Mark Seggel Ph.D. The product quality microbiology reviewer is Steven Donald, M.S.

Dalbavancin is a new molecular entity. It is a semi-synthetic purified lipoglycopeptide antibacterial drug.

The drug substance, dalbavancin hydrochloride is present in two major structural homologs, dalbavancin A and dalbavancin B. Dalbavancin A constitutes about (b) (4) of the drug substance and dalbavancin B constitutes (b) (4) of the drug substance. The drug substance is manufactured at (b) (4)

The drug product, dalbavancin for injection, is a sterile lyophilized powder. Each single use vial contains 500 mg dalbavancin free base, (b) (4) mg mannitol and (b) (4) mg lactose monohydrate. The pH is adjusted to (b) (4) with sodium hydroxide (and/or hydrochloric acid). The drug product is manufactured by (b) (4)

The container closure system consists of a 50 mL Type I glass vial and (b) (4)

Long term stability data (25° C/60% RH) and accelerated stability (40°C/75% RH) data on primary and supporting batches support an expiration period of 36 months at 25° C.

The product quality microbiology reviewer did not identify any deficiencies in the application and recommends approval. The reviewers noted that, in preparing the Master Cell Bank, (b) (4) was used. The applicant has agreed to a postmarketing commitment to replace (b) (4) with a (b) (4). The CMC reviewers have concluded that the applicant has provided sufficient information to assure the identity, strength, quality, purity, potency and bioavailability of dalbavancin. They recommend approval of the NDA pending satisfactory cGMP inspections and issuance of an overall acceptable recommendation from the Office of Compliance.

In an addendum dated May 22, 2014, the CMC reviewers state that the drug substance facility and the drug product facility, as well as one testing laboratory, have been inspected and that the Office of Compliance issued an overall recommendation of acceptable on May 22, 2014. From a CMC perspective, they recommend approval of this NDA.

On May 23, 2014, a memo was filed to the NDA by Steve Hertz from the Division of Good Manufacturing Practice Assessment noting that DGMPA did not concur with the recommendations from the (b) (4) DO) to withhold approval of the NDA

due to product specific deficiencies. DGMPA recommends that corrective actions to the Form 483 should be verified on a follow up inspection.

Based on discussions between DGMPA, (b) (4)-DO, and (b) (4) submitted a response to the deficiencies and a commitment to revise its procedures regarding (b) (4) The information submitted by (b) (4) was acceptable to DGMPA and (b) (4) DO.

A teleconference was also held between the FDA, Durata, and (b) (4) on May 22, 2014 to discuss the above issues and to inform Durata about a postmarketing commitment to provide batch release test results from upcoming PPQ lot(s) once the PPQ activities have been completed. Durata agreed to the postmarketing commitment.

I concur with the recommendations from the CMC reviewers to approve the NDA.

4.0 Pharmacology/Toxicology

The pharmacology/toxicology reviewer for this NDA is Terry Miller Ph.D. During prior review cycles, pharmacology/- toxicology reviews were also conducted by Kenneth Seethaler Ph.D. and Wendelyn Schmidt, Ph.D. In the safety pharmacology studies, dalbavancin had no effect on respiration, body temperature, behavioral and autonomic system parameters. Studies in dogs did not show any effect on cardiac conduction or circulatory parameters. Dalbavancin has a plasma half-life of 1-3 weeks and tissue half-life of ≥ 6 months and persists in the liver and kidneys of animals for extended periods. The toxicity and toxicokinetics of dalbavancin was evaluated after a single dose in mice and rats and after multiple doses in rats (14, 28, and 90 days) and dogs (28 and 90 days). In dogs, dose and rate dependent infusion reactions were observed. Liver and kidney were the primary targets for dalbavancin toxicity; high doses of dalbavancin caused elevated serum transaminases, BUN and creatinine associated with hepatocellular necrosis and renal tubular necrosis, vacuolation and degeneration respectively. The *in vitro* and *in vivo* genetic toxicology studies indicate that dalbavancin was neither mutagenic nor clastogenic. No carcinogenicity studies were conducted as the drug is for short-term use. Dalbavancin was not teratogenic in rats or rabbits. In rats, impaired fertility was not observed at a dose of 15 mg/kg/day (1.2 times the human dose on an exposure basis). Reductions in male and female fertility and increased embryo resorptions occurred at a dose of 45 mg/kg/day (3.5 times the human dose on an exposure basis). At this dose, signs of parental toxicity were also observed**.**

Dr. Miller recommends approval of the NDA from a pharmacology/toxicology perspective. I agree with his assessment.

5.0 Clinical Microbiology

The clinical microbiology reviewer for this NDA is Peter Coderre, PhD, MBA. Dalbavancin is a semi-synthetic, lipoglycopeptide antibacterial drug that interrupts cell wall synthesis by binding to the terminal D-ala-D-ala of cell wall peptidoglycan, thereby preventing cross-linking (transpeptidation and transglycosylation) of disaccharide subunits. Resistance to dalbavancin among Gram-positive bacteria appears to be limited to certain intrinsically glycopeptide-resistant species and to bacteria expressing the VanA phenotype of acquired resistance. Dalbavancin is active against the intrinsically vancomycin-resistant enterococcal species expressing the VanC phenotype and against VanB strains with acquired resistance, but is not active against other intrinsically glycopeptide-resistant Gram-positive bacteria such as pediococci, leuconostocs and some species of lactobacilli. The activity of dalbavancin has been studied *in vitro* and in various animal models of infection. Dr. Coderre's review notes that the applicant had not provided adequate information to support the inclusion of *S. anginosus* group in the indication. Subsequently, the applicant provided additional data to support the inclusion of *S. anginosus* group in the indication, which was found acceptable to Dr. Coderre. Dr. Coderre recommends a susceptible breakpoint of 0.12 mcg/mL for *S. aureus*, *S. pyogenes*, *S. agalactiae* and *S. anginosus*. Dalbavancin disks for diffusion susceptibility testing are not available. Dr. Coderre found the quality controls data for dalbavancin using the dry-format microtiter trays acceptable. The rationale for the susceptibility interpretive criteria is discussed in the following section. Dr. Coderre has recommended two postmarketing requirements (PMRs), one to assess development of resistance to dalbavancin and the second to delineate the mechanism for resistance, if such isolates are identified during the surveillance period. The applicant has agreed to both the PMRs.

I agree with Dr. Coderre's assessment that there are no microbiology issues precluding approval of this NDA.

6.0 Clinical Pharmacology

The clinical pharmacology reviewer for this NDA is Yang He, Ph.D. Most of the pharmacokinetic studies were reviewed during previous review cycles, including studies to assess single and multiple dose pharmacokinetics (PK), excretion and metabolism, penetration into skin blister fluid and impact of renal and hepatic impairment. Additional studies included in this submission are a Phase 1 study to evaluate the PK and safety of a single 1500 mg dose, a thorough QT study and a PK study in adolescent patients 12-16 years of age.

Following single and multiple administrations, the Cmax and AUC of dalbavancin increased proportional to dose. The mean plasma protein binding of dalbavancin is approximately 93%. The drug has a terminal half-life of 346 hours. In *in vitro* studies, dalbavancin was not a substrate or inhibitor of CYP450 isoenzymes. Dalbavancin is excreted in urine and feces. In patients with renal impairment, clearance of dalbavancin was reduced and the AUC was increased compared

to patients with normal renal function. Dalbavancin is not appreciably removed after 3 hours of hemodialysis.

The proposed dosing regimen is 1000 mg of dalbavancin followed one week later by 500 mg, given intravenously. In patients with renal impairment whose known creatinine clearance is less than 30 mL/min and who are not receiving regularly scheduled hemodialysis, the proposed dosing regimen is 750 mg of dalbavancin followed one week later by 375 mg. No dosage adjustment is required for patients receiving regularly scheduled hemodialysis. Dr. Yang considers the proposed dosing regimens acceptable.

Susceptibility Interpretive Criteria:

The applicant proposed a susceptible breakpoint of 0.25 mcg/mL for *S. aureus* and for the streptococcal species that are included in the indications (*S. pyogenes*, *S. agalactiae* and *S. anginosus)*. Drs. He and Coderre recommend a susceptible breakpoint of 0.12 mcg/mL. The following is a summary of the data used to determine susceptibility interpretive criteria for dalbavancin. For details, please refer to the reviews by Drs. He and Coderre.

Animal Models:

During his review, Dr. He noted some inconsistencies in the targets that were used to determine the susceptibility interpretive criteria. Free 24h AUC/MIC (fAUC0-6days/6) was the best PK/PD parameter associated with efficacy in a mouse thigh infection model. However, in Monte Carlo simulations, dalbavancin fAUCinf/MIC and fAUC14day/MIC was used to support target attainment. In response to an information request, the applicant performed reanalysis of nonclinical PK/PD target attainment by incorporating free 24h AUC/MIC of 160 as a static effect target and 266 as a 2-log kill target. Results of this reanalysis support the proposed susceptible breakpoint of 0.25 mcg/mL.

Surveillance Data:

The applicant provided surveillance data from an ongoing worldwide study (2002-2012). The dalbavancin MIC_{90} value for *S. aureus* was 0.06 mcg/mL in 8 of the 11 years of the study and was 0.12 mcg/mL for three years (2007-2009). The MICs ranged from ≤ 0.03 to 0.25 mcg/mL except in 2002, 2004 and 2006 when the upper limit was 0.5 mcg/mL. The dalbavancin MIC_{90} for *S.pyogenes* was ≤0.03 mcg/mL for all years and for *S. agalactiae* it ranged from ≤ 0.03- 0.12 mcg/mL.

Clinical Data:

In Trials DUR001-301 and 302, clinical efficacy data were only available for three patients with *S. aureus* MIC of 0.12 mcg/mL and one patient with *S. aureus* MIC of 0.25 mcg/mL. For clinical

response at 48-72 hours, there were two successes (66.7%) at an MIC of 0.12 mcg/mL and one success (100%) at an MIC of 0.25 mcg/mL. In these two trials, the *S. aureus* MIC was 0.03 or 0.06 mcg/mL in the majority of patients; there were no patients with *S. aureus* MIC of >0.25 mg/mL.

Clinical Pharmacokinetics/Pharmacodynamics (PK/PD):

For the clinical PK/PD analysis, the applicant used PK and efficacy data from Study VER001-09, a previously conducted Phase 3 trial in cSSSI. No PK data were collected in the two new Phase 3 trials. In the univariable PK/PD analysis, the applicant identified a relationship between AUCavg (dalbavancin AUC over 120 hours divided by 5)/MIC and clinical success at Test of Cure (TOC). A threshold of AUCavg/MIC was determined in order to achieve a statistically significant difference in the clinical response rates at TOC between patients above and below the threshold. Dr. He's review notes that the proposed univariable relationships between efficacy endpoints and AUCavg/MIC were mathematically bounded by the percentage of patients < or ≥ AUCavg/MIC threshold; the predicted response rate would not fall below 89.1% for patients with AUCavg/MIC below the threshold with increasing MIC values. Using these results, the mean model-predicted probabilities of clinical response by MIC are shown in the following table:

Table 1: Mean Model-Predicted Probability of Clinical Response

MIC (mcg/mL)	Clinical success at TOC	≥10 % reduction in lesion area Day 4	≥20 % reduction in lesion area Day 4	≥30 % reduction in lesion area Day 4
0.03	100	90.5	85.4	79.6
0.06	96.7	89.6	84.6	78.6
0.12	89.2	77.5	61.4	48.4
0.25	89.1	75.8	53.8	38.5

Source: Table 1.3-2, Clinical Pharmacology Review

In response to an information request from the Division, the applicant noted that given the inherent variability in the PK-PD relationship, the clinical PK-PD analyses based on data from Study VER001-9 may not be appropriate to support a susceptible breakpoint of 0.25 mcg/L for *S. aureus*. The applicant stated that pre-clinical modeling may be more useful at this time relative to modeling based on extrapolations from human data given the challenge of modeling for patients with MICs of 0.12 mcg/mL and 0.25 mcg/mL from the clinical trials. Dr. He concurs with the applicant's position that more weight should be put on the nonclinical PK/PD target

attainment analysis for determining susceptibility interpretive criteria given limitations of the clinical data.

In the applicant's clinical PK/PD modeling, as shown in the table above, the predicted clinical response rate at an MIC of 0.12 mcg/mL was lower than that compared to the clinical response rate predicted at an MIC of 0.06 mcg/mL. Drop off was seen in response rates both for clinical success at TOC and for ≥ 20% reduction in lesion size on Day 4. For ≥ 20% reduction in lesion size at Day 4, the predicted response rates were 84.6% at an MIC of 0.06 mcg/mL and 61.4% at an MIC of 0.12 mcg/mL. Although these analyses support a susceptible breakpoint of 0.06 mcg/mL, data from nonclinical models support a susceptible breakpoint of 0.25 mcg/mL.

Overall, data from nonclinical models, surveillance studies and the limited clinical PK-PD analyses, support a susceptible breakpoint of 0.12 mcg/mL for *S. aureus*. As the PK/PD targets for dalbavancin for streptococci are lower than that for *S. aureus*, a susceptible breakpoint of 0.12 mcg/mL is also acceptable for the streptococcal species included in labeling (*S.pyogenes, S. agalactiae,* and *S. anginosus* group). There was insufficient data to determine interpretive criteria for the intermediate and resistant categories.

I agree with Dr. He and Dr. Coderre that a susceptible breakpoint of 0.12 mcg/mL is acceptable for *S. aureus, S. pyogenes*, *S. agalactiae* and *S. anginosus* group. I do not agree with the mathematical formula used by Dr. Coderre to derive the susceptible breakpoint. All available data from a clinical and nonclinical perspective were taken into consideration along with the overall quality, strengths and weaknesses of each data component in arriving at susceptibility interpretive criteria. At this time, adequate scientific data are not available to support the use of any specific mathematical formula to determine susceptibility interpretive criteria.

Dr. Yang recommends approval of the NDA and I agree with his recommendation.

7.0 Clinical Efficacy/Safety

The clinical reviewer for this NDA is Dmitri Iarikov, M.D. Ph.D., and the statistical reviewer is Christopher Kadoorie PhD.

Efficacy

A total of 21 clinical trials have been conducted with dalbavancin including 14 Phase 1 trials, two Phase 2 trials and five Phase 3 trials. The following three Phase 3 trials were reviewed in the previous review cycles and will not be discussed in this memo:

VER001-8: Uncomplicated skin and soft tissue infections

VER001-9: Complicated skin and soft tissue infections

VER001-16: Complicated or Uncomplicated skin and skin structure infections in patients with suspected or confirmed MRSA

Two new Phase 3 trials, DUR001-301and DUR001-302 were submitted to support the indication of ABSSSI and will be the focus of this review from an efficacy standpoint. Data from all dalbavancin studies are included in the safety analyses.

Trials DUR001-301 and DUR001-302 were double-blind, double-dummy, randomized noninferiority trials comparing two weekly doses of dalbavancin (on Day 1 and Day 8) with vancomycin (with optional switch to oral linezolid) in patients with ABSSSI known or suspected to be caused by Gram-positive bacteria.

Patients were randomized in a 1:1 ratio to receive either two IV doses of dalbavancin (on Day 1 and Day 8) or up to 10 to 14 days of the comparator regimen. Enrollment of patients with major abscesses was capped at 30%. Patients with creatinine clearance (CrCl) ≥30 mL/min and those receiving hemodialysis or peritoneal dialysis received 1000 mg on Day 1 and 500 mg on Day 8. Patients with a CrCl <30 mL/min and not on dialysis received 750 mg on Day 1 and 375 mg on Day 8. Patients in the comparator arm received IV vancomycin with the option to switch to oral linezolid after 72 hours if they met pre-specified criteria. Efficacy and safety assessments were made on Days 2, 3, 4, 8, and 14 or 15 of the treatment period. The short-term follow-up visit (SFU) occurred on Day 26-30 and the long-term follow-up visit (LFU) on Day 60-88.

The primary analysis population was the intention to treat (ITT) population. The primary efficacy endpoint was clinical response (cessation of spread of lesion, and the absence of fever) at 48 to 72 hours. The pre-specified noninferiority margin was 10%. A ≥20% reduction in lesion area from baseline (no fever component) was considered a key secondary endpoint. This primary endpoint is consistent with the recommendations in the draft guidance on ABSSSI issued in 2010.

Based on the recommendations of the Biomarkers Consortium of the Foundation for the National Institutes of Health, a final guidance on ABSSSI was issued in October 2013, that recommends the following endpoints[1,2] :

- Primary Endpoint: Clinical response assessed at 48 to 72 hours defined as ≥ 20 % reduction in lesion size compared to baseline in patients who did not receive rescue therapy and are alive.

[1] Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment.http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071185.pdf

[2] http://www.regulations.gov/#!documentDetail;D=FDA-2010-D-0433-0011

- Key Secondary Endpoint: Resolution of ABSSSI evaluated at 7 to 14 days after completion of therapy.

For this NDA, the pre-specified primary endpoint of cessation of spread of lesion and absence of fever is acceptable and analysis will also be presented for the key secondary endpoint of ≥20% reduction in lesion size.

In both trials, demographic and baseline characteristics were similar between the two treatment groups; most patients were White (~90%). Approximately 36% of patients were enrolled from North America. The major infection type was cellulitis (~50%); the median lesion area was ~ 350 cm^2; > 80% of patients had temperature > 38°C. At least 1 Gram-positive ABSSSI pathogen was isolated in a baseline culture from the primary ABSSSI site or blood culture in ~53% of patients. *S. aureus* was the most commonly identified organism; ~24% of *S. aureus* were methicillin-resistant.

In Trial DUR001-301, 240 (83.3%) patients in the dalbavancin arm and 233 (81.8%) in the comparator arm were responders (95% CI, -4.6, 7.9) at 48-72 hours. In Trial DUR001-302, 285 (76.8%) patients in the dalbavancin arm and 288 (78.3%) in the comparator arm were responders (95% CI, -7.4, 4.6) at 48-72 hours. In both trials, the lower bound of the 95% confidence interval (CI) for the treatment difference was less than 10%. Table 2 provides the results of the two trials for the primary efficacy endpoint.

Table 2:Primary Efficacy Analysis at 48–72 hours (ITT population)

Trial	**Dalbavancin n/N (%)**	**Comparator n/N (%)**	**Treatment difference (95% CI)**
DUR001-301	240/288 (83.3)	233/285 (81.8)	1.5% (-4.6, 7.9)
DUR001-302	285/371 (76.8)	288/368 (78.3)	-1.5% (-7.4, 4.6)
ITT - All randomized patients regardless of receiving study drug.			

Source: Table 18, Medical Officer Review

For the key secondary endpoint of ≥20% reduction in lesion area from baseline (without regard to fever) at 48-72 hours, response rates were approximately 6% to 9% higher in both trials compared to the primary efficacy endpoint of cessation of spread of lesion and the absence of fever at 48 to 72 hours, Table 3.

Table 3: Outcome for the Secondary endpoint of ≥ 20% Reduction in Lesion Area from Baseline at 48–72 hours in the ITT Population

Trial	Dalbavancin n/N (%)	Vancomycin/Linezolid n/N (%)	Treatment difference (95% CI)
DUR001-301	259/288 (89.9)	259/285 (90.9)	-1% (-5.7, 4.0)
DUR001-302	325/371 (87.6)	316/368 (85.9)	1.7% (-3.2, 6.7)

Source: Table 22, Medical Officer Review

Outcomes for the secondary endpoints of clinical status at EOT and SFU visits in the ITT population are presented in Table 4.

In Trial DUR001-301, the response rates in the ITT population at these later endpoints were lower in the dalbavancin arm (81.3% and 86.7% in the dalbavancin and comparator arms, respectively at EOT; 83.7% and 88.1% in the dalbavancin and comparator arms, respectively at the SFU visit).

In Trial DUR001-302, clinical response rates at later endpoints were higher in the dalbavancin arm (88.7% and 85.3% in the dalbavancin and comparator arms, respectively at EOT; 88.1% and 84.5% in the dalbavancin and comparator arms, respectively at the SFU visit).

Table 4: Secondary Clinical Efficacy Endpoint Analysis in Trials DUR001-301 and DUR001-302 (ITT Population)

Endpoint	Dalbavancin n/N (%)	Comparator n/N (%)	Difference (95% CI)
DUR001-301			
Clinical Success at EOT	234/288 (81.3)	247/285 (86.7)	-5.4 (-11.5, 0.6)
Clinical Success at SFU	241/288 (83.7)	251/285 (88.1)	-4.4 (-10.1, 1.4)
DUR001-302			
Clinical Success at EOT	329/371 (88.7)	314/368 (85.3)	3.4 (-1.5, 8.3)
Clinical Success at SFU	327/371 (88.1)	311/368 (84.5)	3.6% (-1.3, 8.7)

Source: Table 23, Medical Officer Review

Dr. Kadoorie concluded that both trials met their primary objectives of demonstrating noninferiority of dalbavancin to comparator therapy based on early clinical response at 48-72 hours using a 10% noninferiority margin. Dr. Kadoorie noted that there was some uncertainty regarding the efficacy at later endpoints such as clinical status at EOT (Day 14-15) and clinical status at the SFU visit (Day 26-30), as the results varied across the two trials, favoring the comparator in Trial DUR001-301 and dalbavancin in Trial DUR001-302. Dr. Kadoorie conducted sensitivity analyses which included additional success criteria considered to be clinically more relevant and concordance analyses which considered findings at later

assessments among patients who were responders at 48-72 hours. Overall, clinical outcomes favored the comparator in Trial DUR001-301 and dalbavancin in Trial DUR001-302.

I agree with the assessment of Drs. Iarikov and Kadoorie that in Trials DUR001-301 and 302, dalbavancin was noninferior to the comparator regimen of vancomycin/linezolid.

Safety

A total of 1778 patients were exposed to one or more doses of dalbavancin in Phase 2 and 3 trials. In Trials DUR001-301 and 302, a total of 652 patients received dalbavancin and 651 patients received comparator.

Across all the Phase 2 and 3 clinical trials, there were 10 deaths (0.6%) in the dalbavancin arm and 15 deaths (1.2%) in the comparator arm. In Trials DUR001-301 and 302, there was one death in the dalbavancin arm and eight deaths in the comparator arm. No deaths were considered related to study drug.

In the dalbavancin arm, 17 (2.6%) patients had a nonfatal serious adverse event (SAE) compared to 29 (4.4%) in the comparator arm. The most common SAEs were in system organ class (SOC) of infections and infestations, 9 (1.4%) events in the dalbavancin arm and 10 (1.5%) in the comparator arm.

Hepatic Effects

In Trials DUR001-301 and -302, six patients with normal baseline ALT had elevation of post-baseline value to >3x upper limit of normal (ULN) in the dalbavancin arm compared to one patient in the comparator arm. In all Phase 2 and 3 clinical trials combined, 12 (0.8%) patients in the dalbavancin arm and two (0.2%) patients in the comparator arm had normal baseline ALT and post baseline elevation of > 3x ULN (Table 5).

Table 5: Post- baseline ALT Elevations of >3x ULN in Patients with Normal Baseline Transaminase Levels

	Trials DUR001-301&302		All Phase 2 and 3 trials	
	Dalbavancin N=505	Comparator N=521	Dalbavancin N=1406	Comparator N=957
> 3x ULN – 5 ULN	3	1	7	1
> 5x ULN – 10x ULN	1	0	2	1
> 10x ULN	2	0	3	0
Total n (%)	6 (1.2)	1 (0.2)	12 (0.8)	2 (0.2)
For trials DUR001-301 and 302, measurements were obtained on Day 3 and at EOT (Day 14-15); for trials VER001-8 and VER001-9, measurements were obtained through the Test of Cure Visit (14 days following the completion of study medication)				

Source: Table 50, Medical Officer Review

ALT transition profiles for the six patients with post-baseline ALT elevation > 3x ULN in Trials DUR001-301 and -302 are presented in Table 6. No patient met Hy's law criteria. One patient, a 47-year-old female with a history of hepatitis C had ALT > 10x ULN and total bilirubin > 4x ULN at the EOT visit, which improved by the follow- up visit. Her baseline alkaline phosphatase level was 124 IU/L. Her history was also confounded by receipt of non-steroidal anti-inflammatory drugs (ketorolac on study day 1 and 2 and metamizole on study day 1).

Table 6: ALT Transition Profiles in Patients with Normal Baseline Transaminases and Post-dose ALT > 3x ULN in Trials DUR001-301 and DUR001-302

Patient ID	ALT levels (normal ranges 0-45 units/L)				
	Baseline	Day 3	EOT [a]	Day 20	Day 27-32
302-737-120	29	28	589	127	-
302-927-428	19	22	622	-	41
302-958-315	33	274	17	-	-
302-747-505	28	31	177	-	-
302-927-051	34	26	175	-	13
302-944-360	11	148	19	-	-

Source: Table 51, Medical Officer Review

Analyses performed by the applicant using potentially clinical significant criteria irrespective of the baseline ALT values across all Phase 2 and 3 trials showed that a slightly higher percentage of dalbavancin-treated patients had ≥ 3 xULN and ≥ 3-fold increase in ALT values on treatment as shown in the table below.

Table 7: Change in Liver Enzymes Based on Potentially Clinical Significant Criteria

Clinical Laboratory Parameter	On Treatment		End of Treatment	
	Dalbavancin	Comparator	Dalbavancin	Comparator
ALT (≥ 3xULN and ≥ 3-fold ↑)	6 (0.5)	1 (0.1)	6 (0.4)	3 (0.3)
AST (≥ 3xULN and ≥ 3-fold ↑)	8 (0.6)	1 (0.1)	3 (0.2)	3 (0.3)
ALP (≥ 1.5xULN and ≥ 2-fold ↑)	8 (0.6)	4 (0.4)	9 (0.6)	6 (0.6)
Total bilirubin (≥ 1.5xULN and ≥ 3-fold ↑)	1 (0.1)	0	2 (0.1)	1 (0.1)

Source: Table 70, Applicant briefing document for the advisory committee meeting[3]

The applicant also provided shift tables by ALT categories across all Phase 2 and 3 trials which showed that 21/210 (10%) patients in the dalbavancin arm moved from a category of ALT>ULN-3xULN at baseline to a higher grade (>3 x ULN) post-baseline. In the comparator arm, 10/169 (5.9%) patients had such a shift. No differences were seen at the end of treatment.

[3] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM390793.pdf

I agree with Dr. Iarikov's recommendation that information regarding the potential for dalbavancin to cause elevation in transaminases be described in the Warnings and Precautions section of the package insert. Overall, it appears that more dalbavancin-treated patients had post-baseline elevations in ALT values, especially in those with normal baseline values. Several of these patients had underlying hepatic conditions, thereby confounding causality assessment. In addition to the imbalance in the frequency of post-baseline ALT elevations in the two new Phase 3 trials, a signal for hepatic effects was noted in previously conducted trials and the liver was identified as a potential target organ of toxicity in nonclinical studies.

Other Safety Issues

In Trial DUR001-302, there was one case of anaphylactoid reaction that was considered related to dalbavancin administration.

In the dalbavancin arm, a total of 214 (32.8%) patients experienced 540 treatment emergent adverse events and in the comparator arm, a total of 247 (37.9%) patients experienced 645 treatment emergent adverse events. The most common adverse events were nausea and headache and were reported in ~ 4% of patients in both arms.

Review of the initial submission of NDA 21883 had identified dalbavancin-associated abnormalities in glucose homeostasis as a potential signal. No increase in abnormalities of glucose homeostasis was seen in the new trials or in all dalbavancin Phase 2 and 3 trials combined.

A thorough QT (TQT) study showed that dalbavancin did not prolong the QT interval. The TQT study was reviewed by the interdisciplinary review team (IRT). The IRT recommended that language regarding the TQT study be included in Section 12.2 (Pharmacodynamics) of labeling.

8.0 Labeling

Hepatic Effects

The Warnings and Precautions section of the package insert includes a warning stating that in patients with normal baseline transaminase levels, more patients in the dalbavancin arm had elevation in ALT values post-baseline compared to those in the comparator arm. Additional information regarding ALT elevations is also included in the adverse reactions section of the package insert.

Hypersensitivity

The Warnings and Precautions section of the package insert includes a warning describing hypersensitivity as a potential adverse reaction based on a report of anaphylactoid reaction seen in a dalbavancin-treated patient.

Labeling reviews were provided by Christine Corser, Pharm D, Office of Prescription Drug Promotion (OPDP) and Aleksander Winiariski, Pharm D, Division of Medication Error Prevention and Analysis (DMEPA). Their recommendations have been incorporated in appropriate sections of the labeling.

9.0 Pediatrics

Under the Pediatric Research and Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless the requirement is waived, deferred or inapplicable. The applicant has submitted a pediatric plan to study pediatric patients 0-18 years of age and has requested a deferral of pediatric studies. The pediatric plan was discussed at the Pediatric review Committee (PeRC) and found to be acceptable. The proposed pediatric studies will be postmarketing requirements.

10.0 Other Regulatory Issues

Clinical Site Inspections

A clinical inspection summary (CIS) report was completed by Lauren Iacono-Connors, PhD, from the Office of Scientific Investigations (OSI) on April 10, 2014. Six clinical sites and the applicant were inspected. Of the six clinical sites, three sites that enrolled patients in Trial DUR001-301 had been closed down by the applicant due to concerns related to study conduct by personnel at the sites. Inspection of the three sites revealed similar significant compliance violations related to records management and drug accountability. Based on the review of preliminary inspectional findings at these sites, OSI initially concluded that data generated by these sites appeared unreliable and recommended that it not be used in the efficacy or safety analyses. Analyses excluding data from these three sites did not affect the overall conclusions from Trial DUR001-301.

On May 6, 2014, in an addendum to the CIS report, Dr. Iacono-Connors provided revised recommendations after complete review of the final establishment inspection reports (EIR). The addendum indicated that the findings from the final EIR were not sufficient to conclude that data from these sites were unreliable. The CIS addendum noted issues with drug transportation records for the three sites, but stated “there is evidence that the drug was prepared and

administered to the patients". The report indicated the unreliable drug transportation records should not affect data integrity. It was also noted that drug administration records were missing for 6 of 16 patients at one of the clinical sites (Site 118) and that the Division may consider checking to see if these patients completed the study and were considered in the analysis population. If they were, the Division could consider excluding these patients from analysis, since there is no source documentation to confirm that the drug was administered. Alternatively, the Division might assess the treatment received by each of the six patients, and if treatment is randomly distributed between the test article and active control, the missing infusion records were unlikely to impact the interpretation of Trial DUR001-301.

All five dalbavancin-treated patients were considered successes in the primary and secondary outcomes and the one vancomycin patient was considered a failure for the primary endpoint, but success for the secondary endpoint of ≥20% reduction in lesion size. As the missing drug administration records in these six patients are not likely to affect data integrity, these data were not excluded from the overall analyses. Analysis of data excluding data from these six patients did not affect the overall conclusions for Trial DUR001-301. These six patients are included in the ITT population.

Advisory Committee Meeting

This NDA was discussed by the Anti-Infective Drugs Advisory Committee on March 30, 2014. The following question was posed to the committee:

Question

Has the applicant provided substantial evidence of the safety and effectiveness of dalbavancin for the treatment of acute bacterial skin and skin structure infections caused by susceptible isolates of the designated microorganisms?

a. If yes, please provide any recommendations concerning labeling.

b. If no, what additional studies/analyses are needed?

There were 12 votes in favor and none against.
The advisory committee meeting minutes are available at:

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM396637.pdf

11.0 Risk Management

Robert Pratt, Pharm D, was the reviewer from the Division of Risk Management. Dr. Pratt concluded that based on the available data and the potential benefits and risks, a REMS requirement cannot be established. I agree with Dr. Pratt's assessment. Adverse reactions have been adequately addressed in labeling and will be monitored in routine pharmacovigilance.

Post Marketing Commitments (PMCs) and Post Marketing Requirements (PMRs)

The applicant has agreed to the following PMRs and PMCs:

PEDIATRIC POSTMARKETING REQUIREMENTS:

1. Conduct a single dose pharmacokinetic (PK) study in children from 3 months to less than 12 years of age.
2. Conduct a single dose PK study in neonates/infants from 0 to less than 3 months of age.
3. Conduct a Phase 3, randomized, comparator-controlled study of dalbavancin in children from 3 months to 17 years of age with ABSSSI.
4. Conduct a Phase 3, randomized, comparator-controlled study of dalbavancin in neonates/infants from birth to less than 3 months of age with ABSSSI.

POSTMARKETING REQUIREMENTS UNDER 505(o):

1. Conduct US surveillance studies for five years from the date of marketing dalbavancin to determine if resistance to dalbavancin has developed in those organisms specific to the indication in the label for ABSSSI.
2. Conduct studies to define the mechanism(s) of resistance for isolates identified as being resistant to dalbavancin during the surveillance period (five years from the date of marketing).

POSTMARKETING COMMITMENTS:

1. Replace (b) (4) used for preparing the Master Cell Bank with a (b) (4)
2. Submit batch release test results from upcoming process performance qualification lot(s) when process performance qualification activities have been completed.

12.0 Recommended Regulatory Action

I agree with the review team that the applicant has provided adequate information to support the safety and effectiveness of dalbavancin for the treatment of adults with acute bacterial skin and skin structure infections. Dalbavancin was noninferior to the comparator regimen in two adequate and well-controlled Phase 3 trials. The main safety concerns of elevated transaminases and hypersensitivity reactions are adequately addressed in the Warnings and Precautions and Adverse Reactions sections of the package insert. I recommend approval of this NDA.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUMATHI NAMBIAR
05/23/2014